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(71) Applicant *(for all designated States except US)*: CENTRAL RESEARCH LABORATORIES LIMITED [GB/GB]; Dawley Road, Hayes, Middlesex UB3 1HH (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: HOLCROFT, Brian [GB/GB]; 35 Six Penny Lane, Chalgrove, Oxon OX44 7YD (GB).

(74) Agent: LEAMAN, Keith; QED Patents Limited, Dawley Road, Hayes, Middlesex UB3 1HH (GB).

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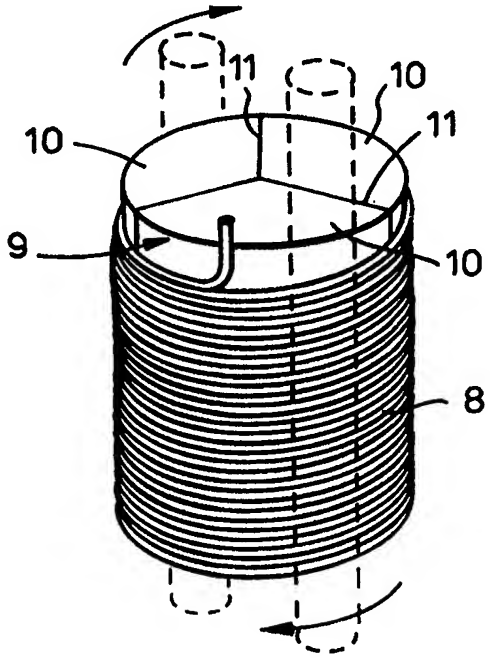
(57) Abstract

A heating apparatus for repeated thermal cycling of a sample comprises a cylindrical block (9) having two or more segments (10) each of which can be heated to a predetermined temperature. A tube (8) is provided for holding a sample physically disposed in thermal contact with the block (9). Movement of the sample within the tube means (8) causes sequential and cyclic exposure of the sample to heated segments (10) of the block (9) and thereby to different temperature cycles.



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HEATING APPARATUS

The present invention relates to heating apparatus, particularly though not exclusively for PCR (polymerase chain reaction) amplification.

A well known requirement for PCR amplification is a rapid thermal cycling, perhaps as many as 30 times through predetermined temperature profiles. This needs to be achieved rapidly, repeatably and uniformly. Furthermore it is desirable to confine the sample and reagents in a disposable, low cost item. Additionally, the instrumentation required to heat-cycle the sample should be as simple as possible to aid reliability, reduce cost and facilitate portable use.

WO9005023-A discloses a heating arrangement for PCR amplification wherein the temperature of a sample can be set optionally to different values by a block which holds the sample being movable along a dovetail groove between different temperature zones thermostatically controlled at different temperatures by two or three elements adjacent to the block.

FR2672231-A1 discloses heating apparatus for automatically performing repeated heating cycles for treating a biological sample wherein the sample can be moved, inside a flexible, capillary between at least two temperature controlled zones, a system for driving the sample consisting of two rollers compressing the capillary and moving along the capillary to drive the sample.

A disadvantage of both of the above systems is that a movable carriage is required for transporting the sample, which increase costs considerably, increases thermal cycling times, and increase difficulties of good thermal connection to the sample.

The present invention provides heating apparatus for repeated thermal cycling of a sample, characterised in that the apparatus comprises a cylindrical block having two or more segments which can be heated to different temperatures, and a tube means for holding a sample physically disposed in relation to the block so that movement of a sample within the tube means relative to the block causes sequential and cyclic exposure of the sample to the segments of the block at different temperatures.

There is thus provided in accordance with the invention, a simple and inexpensive means for rapidly cycling a sample repeatedly through temperature cycles.

The present invention will now be described, by way of examples, with reference to the accompanying drawings in which:

Figures 1 to 6 illustrates six embodiments of the invention.

Referring to Figure 1 there is shown a heating apparatus comprising a tube wound 8 helically around a static cylindrical heating block 9. Pressure and/or gravity, or other means forces the sample through tube 8 and around the heating block 9. In greater detail, the heating block 9 comprises two or more, but ideally three, individual segments 10 separated by thermally insulators 11. Each segment 10 is heated electrically and held at the appropriate temperature. The sample is introduced into the helical tube 8 which is positioned around the heating cylinder 9 in close thermal contact with the outside faces of the segments 10. The sample is then forced through the tube arrangement, thus passing sequentially from one temperature zone defined by each segment 10 to the next. The number of cycles is controlled by the length of the tube 8, the diameter of the heating cylinder 9 and the number of turns of the coil. Typically 1m of tubing on a 1cm diameter heating mandrel produces approximately 30 turns.

In the embodiment of Figure 1 the tube 8 may be made of an elastically deformable material and one or more elongate bars 12 (shown schematically as dotted lines in Figure 1 extending parallel to the longitudinal axis of the cylinder 9. The bars are urged radially inwards against the tube 8 to compress the tube 8 against the cylinder 9 and trap a plurality of samples within the tube 8 between the regions pinched by the bars 12. Rotation of the bars 12 bodily around the axis of the heater cylinder 9 will transport the trapped samples around a helical path from an inlet of tube 8 to an outlet of the tube. Each sample thereby undergoes repetitive thermal cycling.

In a second embodiment, shown in Figure 2 a sample is held within a section of a deformable tube means 8 by, for example, pinch rollers 13 clamping the ends of the section, and the cylindrical block 9 constructed similar to that shown in Figure 1 is rotated while in contact with the tube means in order to thermally cycle the sample. There may be a plurality of sections of tube 8 side-by-side along the length of the block 9 each of which extends around part of the circumfrence of the block 9. In this way a plurality of samples can be processed simultaneously.

The embodiment shown in Figure 2, reduces the length of tubing required, and so minimises contamination by the tubing. It will be seen from Figure 2 that only a short length of tubing 8 is held in contact with a rotating segment heater 9 by the pinch rollers

13. The heater 9 is rotated the requisite number of times to cycle the sample through the appropriate temperature regimes. Using this method, various dwell times could be introduced by changing the rotation speed of the heater 9.

Figure 3 shows a modification of the embodiment shown in Figure 2 in which two rotating heater cylinders 15, 16 constructed similar to the are used to improve the uniformity of the temperature profile in the sample. Here again, pinch rollers 13 are used to trap samples in the tube 8 during the thermal cycling.

Figure 4 shows the use of multiple pairs of contra rotating heaters 18, 19, 20 each constructed similar to the heater block 9 of Figure 1 to process multiple samples, using different temperature profiles. In a further alternative embodiment the outer two pairs of drums 18, 20 could be used to pump the samples into and away from the region of the heater cylinder 19.

Figure 5 shows a further embodiment similar to that of Figure 1 but using a disposable components. The sample is introduced into a top pouch 21 where it can be mixed with required reagents and the pouch sealed. The sample can then be driven through the tubing 8 either using air pressure applied to the outside of the top pouch 21 to compress the pouch 21 or forced through the tube 8 by rolling up the pouch 21 (as shown in Figure 6). When the sample has travelled through the tube 8 it can be collected in a sealed lower pouch 22. The concept of using disposable pouches as shown in figures 5 and 6 could be applied to the embodiments shown in Figures 2 to 4.

Referring to Figure 7 there is shown a further embodiment in which the device shown in Figure 1 is provided with an outer heater ring 24 comprising three segments 25, 26, 27 which are heated to the same temperature as that defined by the segments of the heater block 9 located radially inside the outer segments.

It is to be understood that further embodiments of the invention are possible. For example

the outside faces of the heating cylinder 9 can be profiled to increase the thermal contact between the tube 8 and the heater block 9. For example the cylinder 9 may have a semi circular cross section groove corresponding to the cross sectional shape of the tube 8.

The inner faces of the segments 25, 26, 27 of the concentric outer ring 24 shown in Figure 7 are preferably profiled to improve thermal conductivity between the segments and the tube 8.

The use of radially moveable segments 11 and/or 25, 26, 27 (similar to a drill chuck) may be used to improve thermal contact between heater 9 and tube 8 and facilitate easy loading of the device.

CLAIMS

1. A heating apparatus for repeated thermal cycling of a sample, characterised in that the apparatus comprises a cylindrical block (a) having two or more segments 10 each which can be heated to different temperatures, and a tube (8) for holding a sample physically disposed in relation to the block (a) so that movement of a sample within the tube means (8) relative to the block (9) causes sequential and cyclic exposure of the sample to the segments (10) of the block (9) at different temperatures.

2. A heating apparatus according to claim 1, wherein the block (9) has three heated segments (10) held at respective temperatures.

3. A heating apparatus according to claim 1 or 2, including thermal insulating means (11) disposed between the segments.

4. A heating apparatus according to any preceding claim, wherein the tube (8) is a helically wound around the cylindrical block (9).

5. A heating apparatus according to claim 3, including means (12, 21)for forcing the sample through the tube (8).

6. A heating apparatus according to claim 3, including means (12, 21) for forcing a fluid through the tube (8).

7. A heating apparatus according to claim 6, wherein the tube (8) has a flexible sealable pouch (21, 22) at each end, pressure applied to one pouch (21) forcing the sample through the tube (8) to the other pouch (22).

8. A heating apparatus according to claim 1, wherein the cylindrical block (9) and/or tube (8) have complementary profiles for making good thermal contact.

9. A heating apparatus according to claim 1, wherein a length of tube (8) is held between pairs of rollers (13) and in contact with one or more of said cylindrical blocks (9) which are rotatable in order to provide thermal cycling of the sample.

10. A heating apparatus according to claim 1 wherein there is provided a plurality of pairs of contra-rotating cylindrical blocks (9) each of which has two more more segments (10) which can be heated to different temperatures, and the tube (8) extends between the nip of each pair of contra-rotating blocks (9).

11. A heating apparatus according to claim 1 wherein there is provided an outer heater ring (24) which comprises a plurality of outer segments (25, 26, 27) each of which can be heated to different temperatures, and said outer segments (25, 26, 27) are positioned in thermal contact with the tube 8.

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12. Heating apparatus substantially as described with reference to any one of the accompanying drawings.

Fig.1.

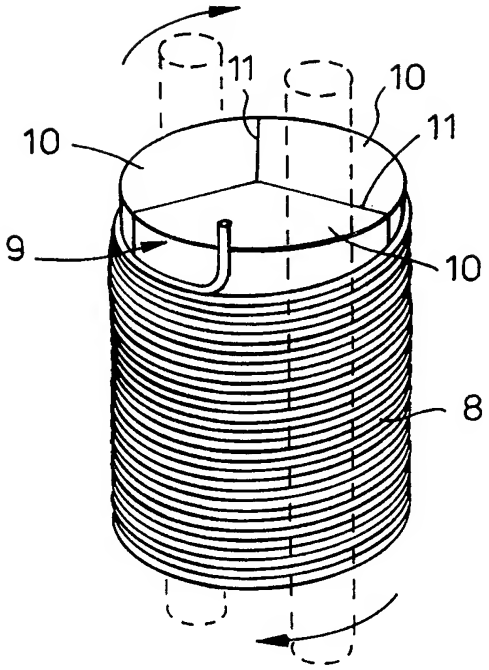


Fig.2.

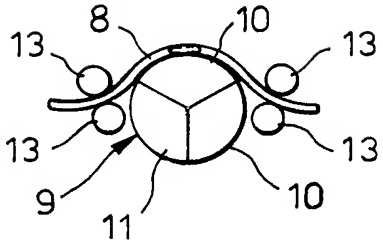


Fig.3.

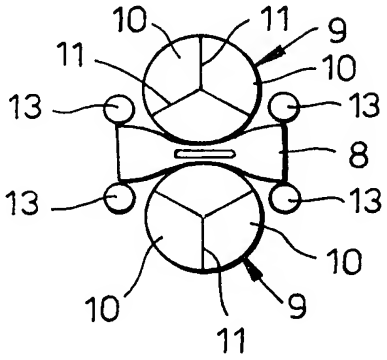


Fig.4.

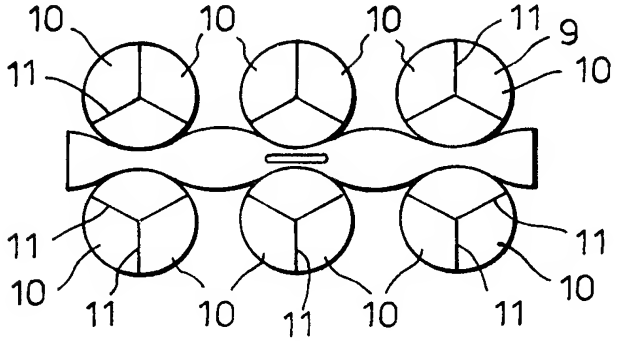


Fig.5.

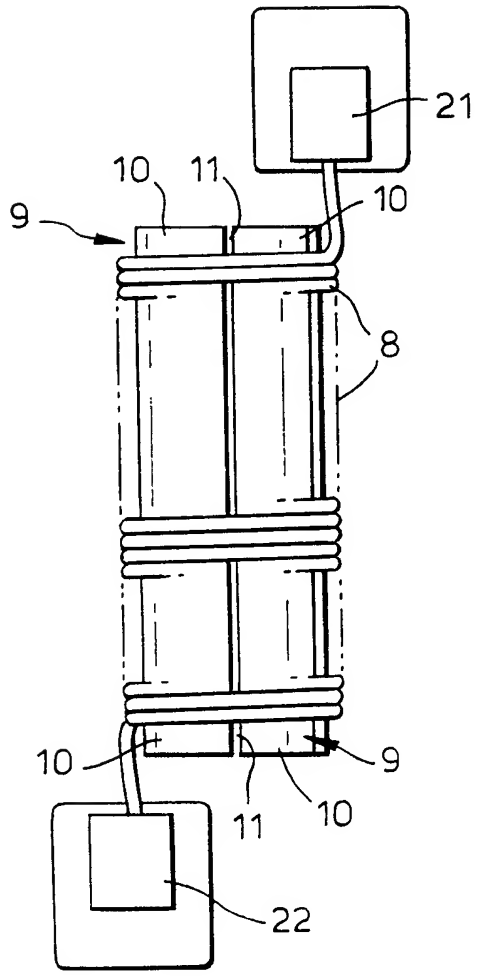


Fig.6.

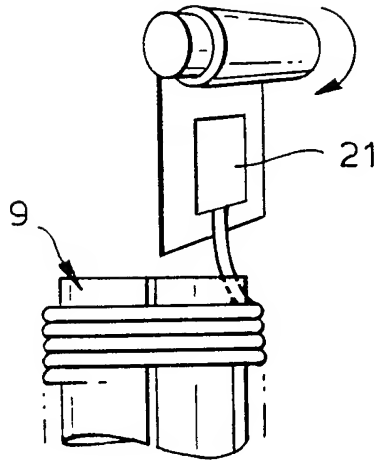
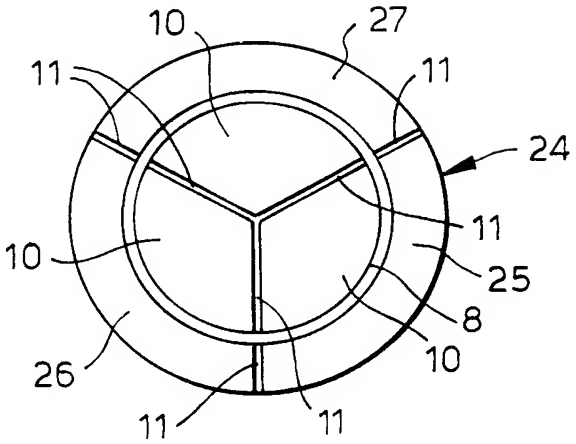


Fig.7.



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01L7/00 B01J19/22 G05D23/19 //C12Q1/68

According to International Patent Classification(IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01L G01N B01J G05D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 664 178 A (SPERGEL PHILIP ET AL) 23 May 1972 see column 2, line 22 - column 4, line 17; figures 3-5 ---	1,8,11
X	FR 2 650 657 A (SCRAS SA) 8 February 1991 see page 5, line 18 - page 6, line 24 see page 7, line 9-32 see page 10, line 1 - line 8; figures 1-3 ---	1-3,5-8, 11
X	EP 0 488 942 A (AIRMOTEC AG) 3 June 1992 see page 3, line 34 - line 40 see page 3, line 47 - line 50 see page 3, line 52 - page 4, line 13 see figures 1-4 --- -/--	1,4,8

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 January 1998	30/01/1998

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A	FR 2 672 231 A (EIBET) 7 August 1992 cited in the application see abstract; claims 1-5; figures 1,2	1-3,5,6, 8
A	WO 90 05023 A (MAX PLANCK GESELLSCHAFT) 17 May 1990 cited in the application see abstract; claims 1-3,9,10; figures 1,2	1-3,5,6, 8,11

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INVENTOR-INFORMATION:

NAME	COUNTRY
HOLCROFT, BRIAN	GB

ASSIGNEE-INFORMATION:

NAME	COUNTRY
CENTRAL RESEARCH LAB LTD	GB
HOLCROFT BRIAN	GB

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ABSTRACT:

CHG DATE=19990617 STATUS=O>A heating apparatus for repeated thermal cycling of a sample comprises a cylindrical block (9) having two or more

segments (10) each of which can be heated to a predetermined temperature. A tube (8) is provided for holding a sample physically disposed in thermal contact with the block (9). Movement of the sample within the tube means (8) causes sequential and cyclic exposure of the sample to heated segments (10) of the block (9) and thereby to different temperature cycles.